

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C12Q 1/68</b>		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/06769</b>
			<b>(43) International Publication Date:</b> 10 February 2000 (10.02.00)
<b>(21) International Application Number:</b> PCT/GB99/02341		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
<b>(22) International Filing Date:</b> 20 July 1999 (20.07.99)		<b>Published</b> <i>With international search report.</i>	
<b>(30) Priority Data:</b> 9816193.8 25 July 1998 (25.07.98) GB 9901844.2 28 January 1999 (28.01.99) GB		<b>(88) Date of publication of the international search report:</b> 11 May 2000 (11.05.00)	
<b>(71) Applicant (for all designated States except US):</b> ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).			
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SMITH, John, Craig [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). ANAND, Rakesh [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MORTEN, John, Edward, Norris [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			
<b>(74) Agent:</b> GILES, Allen, Frank; AstaZeneca PLC, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			
<b>(54) Title:</b> HUMAN CCR-2 GENE POLYMORPHISMS			
<b>(57) Abstract</b> <p>This invention relates to polymorphisms in the human CCR-2 gene, in particular to the discovery of two polymorphisms in the coding sequence of the CCR-2 gene and 11 polymorphisms in the promoter sequence of the CCR-2 gene. The invention also relates to methods and materials for analysing allelic variation in the CCR-2 gene, and to the use of CCR-2 polymorphism in the diagnosis and treatment of CCR-2 ligand mediated diseases such as rheumatoid arthritis and other inflammatory diseases.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# INTERNATIONAL SEARCH REPORT

Int lional Application No  
PCT/GB 99/02341

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 01, 30 January 1998 (1998-01-30) & JP 09 238688 A (TAKEDA CHEM IND LTD), 16 September 1997 (1997-09-16)	4
Y	* see especially nucleotides at polymorphic positions 780 and 1044 * abstract; figure 1	1-3,5,6, 8-11
X	SMITH ET AL: "Contrasting genetic influence of CCR2 and CCR5 variants on HIV -1 infection and disease progression" SCIENCE, vol. 277, 15 August 1997 (1997-08-15), pages 959-965, XP002099015 ISSN: 0036-8075	5,6
Y	* see especially point 31 of the notes * the whole document	1,2
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

22 February 2000

Date of mailing of the international search report

07.03.2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Knehr, M

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/GB 99/02341

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOSTRIKIS ET AL: "A chemokine receptor CCR2 allele delays HIV -1 disease progression is associated with a CCR5 promoter mutation" NATURE MEDICINE, vol. 4, no. 3, March 1998 (1998-03), pages 350-353, XP002099017 ISSN: 1078-8956 cited in the application	5,6
Y	the whole document	1,2
X	WONG L-M ET AL.: "Organization and differential expression of the human monocyte chemoattractant protein 1 receptor gene" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 2, 1997, pages 1038-1045, XP002121129 cited in the application the whole document & DATABASE GENBANK 'Online! Accession number (AC): U80923, 1997 WONG L M ET AL.: "Organization and differential expression of the human monocyte chemoattractant protein 1 receptor gene" * see especially nucleotides at polymorphic positions 42673 and 42874 * abstract	4
X	DATABASE GENBANK 'Online! Accession number (AC): T40384, 1995 HILLIER L ET AL.: "The WashU-Merck EST project" XP002131229 * see especially nucleotides at polymorphic position 41768 * abstract	4
Y	SOZZANI S ET AL: "MCP -1 and CCR2 in HIV infection: regulation of agonist and receptor expression" JOURNAL OF LEUKOCYTE BIOLOGY, vol. 62, July 1997 (1997-07), pages 30-33, XP002099019 ISSN: 0741-5400 the whole document	8-10
Y	US 5 707 815 A (CHARO ISRAEL F ET AL) 13 January 1998 (1998-01-13) cited in the application the whole document	8-10

-/--

# INTERNATIONAL SEARCH REPORT

Int tional Application No  
PCT/GB 99/02341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MUMMIDI S ET AL.: "Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression" NATURE MEDICINE, vol. 4, no. 7, 1998, pages 786-793, XP002121126 abstract page 786, column 1, paragraph 1 -column 2, paragraph 2 page 789, column 2, paragraph 2 -page 792, column 2, paragraph 3; figure 1; tables 1-3	1,5,6
Y	WO 97 40462 A (SPECTRA BIOMEDICAL INC) 30 October 1997 (1997-10-30) cited in the application the whole document	11
Y	NEWTON C R ET AL: "ANALYSIS OF ANY POINT MUTATION IN DNA. THE AMPLIFICATION REFRACTORY MUTATION SYSTEM (ARMS)" NUCLEIC ACIDS RESEARCH, vol. 17, no. 7, 11 April 1989 (1989-04-11), pages 2503-2516, XP000141596 ISSN: 0305-1048 the whole document	1,3
A	ANZALA A O ET AL.: "CCR2-64I allele and genotype association with delayed AIDS progression in african women" THE LANCET, vol. 351, 1998, pages 1632-1633, XP002121127 the whole document	
A	RIZZARDI G P ET AL.: "CCR2 polymorphism and HIV disease" NATURE MEDICINE, vol. 4, no. 3, 1998, pages 252-253, XP002121128 the whole document	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02341

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/02341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 09238688 A	16-09-1997	NONE	
US 5707815 A	13-01-1998	AU 1679395 A EP 0740701 A JP 9508264 T WO 9519436 A	01-08-1995 06-11-1996 26-08-1997 20-07-1995
WO 9740462 A	30-10-1997	AU 2734197 A EP 0897567 A	12-11-1997 24-02-1999

Copy for the Elected Office (EO/US)  
**PATENT COOPERATION TREATY**

PCT/GB99/02341

**PCT**

From the INTERNATIONAL BUREAU

**NOTIFICATION OF THE RECORDING  
OF A CHANGE**

(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

GILES, Allen, Frank  
AstraZeneca UK Limited  
Global Intellectual Property  
Mereside, Alderley Park  
Macclesfield  
Cheshire SK10 4TG  
ROYAUME-UNI

Date of mailing (day/month/year) 29 September 2000 (29.09.00)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference PHM 70363/WO	
International application No. PCT/GB99/02341	International filing date (day/month/year) 20 July 1999 (20.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address ASTRAZENECA Global Intellectual Property P.O. Box 272 Mereside, Alderley Park Macclesfield Cheshire SK10 4GR United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☐ the International Searching Authority ☒ the elected Offices concerned  
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Jean-Marie McAdams Telephone No.: (41-22) 338.83.38
---	--



## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

GILES, Allen, Frank  
AstraZeneca UK Limited  
Global Intellectual Property  
Mereside, Alderley Park  
Macclesfield  
Cheshire SK10 4TG  
ROYAUME-UNI

Date of mailing (day/month/year)

05 May 2000 (05.05.00)

Applicant's or agent's file reference

PHM 70363/WO

International application No.

PCT/GB99/02341

## IMPORTANT NOTIFICATION

International filing date (day/month/year)

20 July 1999 (20.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

ZENECA LIMITED  
15 Stanhope Gate  
London W1Y 6LN  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

ASTRAZENECA UK LIMITED  
15 Stanhope Gate  
London W1Y 6LN  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☐ the International Searching Authority ☒ the elected Offices concerned  
☒ the International Preliminary Examining Authority ☐ other:

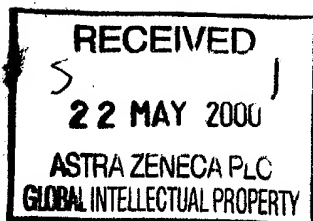
The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Ellen Moyse

Telephone No.: (41-22) 338.83.38



PATENT COOPERATION TREATY

23 MAY 2000 PCT/GB99/02341

PCT

From the INTERNATIONAL BUREAU

To:

GILES, Allen, Frank  
AstraZeneca UK Limited  
Global Intellectual Property  
Mereside, Alderley Park  
Macclesfield  
Cheshire SK10 4TG  
ROYAUME-UNI

NOTIFICATION OF THE RECORDING  
OF A CHANGE

(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 05 May 2000 (05.05.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PHM 70363/WO	
International application No. PCT/GB99/02341	International filing date (day/month/year) 20 July 1999 (20.07.99)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

ZENECA LIMITED  
15 Stanhope Gate  
London W1Y 6LN  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

ASTRAZENECA UK LIMITED  
15 Stanhope Gate  
London W1Y 6LN  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☐ the International Searching Authority ☒ the elected Offices concerned  
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Ellen Moyse

Telephone No.: (41-22) 338.83.38

# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) PHM 70363/WO

### Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

### Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ZENECA Limited  
15 Stanhope Gate  
LONDON  
GB-W1Y 6LN  
GB

☐ This person is also inventor.

Telephone No.  
(01625) 516173

Facsimile No.  
(01625) 583358

Teleprinter No.  
669095/669388

State (that is, country) of nationality:  
GB

State (that is, country) of residence  
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

### Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SMITH, John Craig  
Alderley Park  
Macclesfield  
Cheshire  
GB-SK10 4TG  
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

### Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

GILES, Allen Frank  
Global Intellectual Property  
AstaZeneca PLC  
Mereside, Alderley Park  
Macclesfield, Cheshire, GB-SK10 4TG, GB

Telephone No.  
(01625) 516573

Facsimile No.  
(01625) 583358

Teleprinter No.  
669095/669388

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

## Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ANAND, Rakesh  
Alderley Park  
Macclesfield  
Cheshire  
GB-SK10 4TG  
GB

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MORTEN, John Edward Norris  
Alderley Park  
Macclesfield  
Cheshire  
GB-SK10 4TG  
GB

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant  
for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

**Regional Patent**

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line) .....


**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> AL Albania .....                               | <input checked="" type="checkbox"/> LS Lesotho .....                                   |
| <input checked="" type="checkbox"/> AM Armenia .....                               | <input checked="" type="checkbox"/> LT Lithuania .....                                 |
| <input checked="" type="checkbox"/> AT Austria .....                               | <input checked="" type="checkbox"/> LU Luxembourg .....                                |
| <input checked="" type="checkbox"/> AU Australia .....                             | <input checked="" type="checkbox"/> LV Latvia .....                                    |
| <input checked="" type="checkbox"/> AZ Azerbaijan .....                            | <input checked="" type="checkbox"/> MD Republic of Moldova .....                       |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina .....                | <input checked="" type="checkbox"/> MG Madagascar .....                                |
| <input checked="" type="checkbox"/> BB Barbados .....                              | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia ..... |
| <input checked="" type="checkbox"/> BG Bulgaria .....                              | <input checked="" type="checkbox"/> MN Mongolia .....                                  |
| <input checked="" type="checkbox"/> BR Brazil .....                                | <input checked="" type="checkbox"/> MW Malawi .....                                    |
| <input checked="" type="checkbox"/> BY Belarus .....                               | <input checked="" type="checkbox"/> MX Mexico .....                                    |
| <input checked="" type="checkbox"/> CA Canada .....                                | <input checked="" type="checkbox"/> NO Norway .....                                    |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein .....  | <input checked="" type="checkbox"/> NZ New Zealand .....                               |
| <input checked="" type="checkbox"/> CN China .....                                 | <input checked="" type="checkbox"/> PL Poland .....                                    |
| <input checked="" type="checkbox"/> CU Cuba .....                                  | <input checked="" type="checkbox"/> PT Portugal .....                                  |
| <input checked="" type="checkbox"/> CZ Czech Republic .....                        | <input checked="" type="checkbox"/> RO Romania .....                                   |
| <input checked="" type="checkbox"/> DE Germany .....                               | <input checked="" type="checkbox"/> RU Russian Federation .....                        |
| <input checked="" type="checkbox"/> DK Denmark .....                               | <input checked="" type="checkbox"/> SD Sudan .....                                     |
| <input checked="" type="checkbox"/> EE Estonia .....                               | <input checked="" type="checkbox"/> SE Sweden .....                                    |
| <input checked="" type="checkbox"/> ES Spain .....                                 | <input checked="" type="checkbox"/> SG Singapore .....                                 |
| <input checked="" type="checkbox"/> FI Finland .....                               | <input checked="" type="checkbox"/> SI Slovenia .....                                  |
| <input checked="" type="checkbox"/> GB United Kingdom .....                        | <input checked="" type="checkbox"/> SK Slovakia .....                                  |
| <input checked="" type="checkbox"/> GD Grenada .....                               | <input checked="" type="checkbox"/> SL Sierra Leone .....                              |
| <input checked="" type="checkbox"/> GE Georgia .....                               | <input checked="" type="checkbox"/> TJ Tajikistan .....                                |
| <input checked="" type="checkbox"/> GH Ghana .....                                 | <input checked="" type="checkbox"/> TM Turkmenistan .....                              |
| <input checked="" type="checkbox"/> GM Gambia .....                                | <input checked="" type="checkbox"/> TR Turkey .....                                    |
| <input checked="" type="checkbox"/> HR Croatia .....                               | <input checked="" type="checkbox"/> TT Trinidad and Tobago .....                       |
| <input checked="" type="checkbox"/> HU Hungary .....                               | <input checked="" type="checkbox"/> UA Ukraine .....                                   |
| <input checked="" type="checkbox"/> ID Indonesia .....                             | <input checked="" type="checkbox"/> UG Uganda .....                                    |
| <input checked="" type="checkbox"/> IL Israel .....                                | <input checked="" type="checkbox"/> US United States of America .....                  |
| <input checked="" type="checkbox"/> IN India .....                                 | <input checked="" type="checkbox"/> UZ Uzbekistan .....                                |
| <input checked="" type="checkbox"/> IS Iceland .....                               | <input checked="" type="checkbox"/> VN Viet Nam .....                                  |
| <input checked="" type="checkbox"/> JP Japan .....                                 | <input checked="" type="checkbox"/> YU Yugoslavia .....                                |
| <input checked="" type="checkbox"/> KE Kenya .....                                 | <input checked="" type="checkbox"/> ZW Zimbabwe .....                                  |
| <input checked="" type="checkbox"/> KG Kyrgyzstan .....                            |  |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea ..... |  |
| <input checked="" type="checkbox"/> KR Republic of Korea .....                     |  |
| <input checked="" type="checkbox"/> KZ Kazakhstan .....                            |  |
| <input checked="" type="checkbox"/> LC Saint Lucia .....                           |  |
| <input checked="" type="checkbox"/> LK Sri Lanka .....                             |  |
| <input checked="" type="checkbox"/> LR Liberia .....                               |  |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ AE United Arab Emirates .....
- ☒ South Africa .....
- ☐ .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

<b>Box No. VI PRIORITY CLAIM</b>		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 25-Jul-98 (25.07.98)	9816193.8	GB		
item (2) 28-Jan-99 (28.01.99)	9901844.2	GB		
item (3)				
<input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):				
* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.				
<b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>				
<b>Choice of International Searching Authority (ISA)</b> (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		<b>Request to use results of earlier search; reference to that search</b> (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA /		Date (day/month/year)	Number	Country (or regional Office)
<b>Box No. VIII CHECK LIST; LANGUAGE OF FILING</b>				
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 26 claims : 3 abstract : 1 drawings : sequence listing part of description : 4 Total number of sheets : 38		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):		
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: ENGLISH		
<b>Box No. IX SIGNATURE OF APPLICANT OR AGENT</b>				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).				
				
GILES, Allen Frank AGENT				

For receiving Office use only	
1. Date of actual receipt of the purported international application:  3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:  4. Date of timely receipt of the required corrections under PCT Article 11(2):  5. International Searching Authority (if two or more are competent): ISA /	2. Drawings:  <input type="checkbox"/> received:  <input type="checkbox"/> not received:  6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

# PATENT COOPERATION TREATY

# PCT

REC'D 09 NOV 2000

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>PHM 70363/WO</b>		<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/GB99/02341</b>	International filing date (day/month/year) <b>20/07/1999</b>	Priority date (day/month/year) <b>25/07/1998</b>		
International Patent Classification (IPC) or national classification and IPC <b>C12Q1/68</b>				
Applicant <b>[ZENECA LIMITED et al.] ASTRAZENECA UK LIMITED</b>				

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>27/01/2000</b>	Date of completion of this report <b>07.11.2000</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer <b>Tilkorn, A-C</b>  Telephone No. <b>+49 89 2399 8688</b>



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02341

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-26 as originally filed

**Claims, No.:**

1-11 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 8 and 11 with respect to industrial application.

because:

- ☒ the said international application, or the said claims Nos. 8 and 11 relate to the following subject matter which does not require an international preliminary examination (*specify*):



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02341

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02341

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-3,5-8
	No:	Claims	4,9-11
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	-

**2. Citations and explanations**

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

**Section I:**

This Preliminary Report also takes into consideration pages 1-4 of the Sequence Listing (i.e information concerning SEQ ID NOs 1-14).

**Section III:**

For the assessment of the present **claim 8** on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Claim 11** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT since it amounts to mere presentation of information (Guidelines IV-2.4(e)).

Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of **claims 8 and 11** (Article 34(4)(a)(i) PCT).

**Section IV:**

"A priori" the application contains two separate inventions:

1. The diagnosis of CCR-2 polymorphic sequences, primers and probes (**claims 1-7, claim 8 (partially) and claim 11**).
2. CCR-2 ligand antagonist drugs and their use (**claim 8 (partially), claims 9 and 10**).

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

The first invention provides a method for the diagnosis of CCR-2 polymorphisms  
The second invention solves the problem of treating a CCR-2 ligand mediated disease.

Throughout the application there is no indication found which would link a certain polymorphic CCR-2 allele to a CCR-2 ligand mediated disease. Hence, the effect of CCR-2 ligand antagonists (invention 2) is not dependent on the polymorphic CCR-2 allele detected in the first invention. Thus, the two inventions do not share a special technical feature.

Furthermore, in view of the prior art, the first invention as defined above (**Claims 1-7, 8 (partially) and 11**) is split up into the 13 polymorphisms and the corresponding primers, probes and methods (lack of unity "a posteriori")(Rule 13.2 PCT):

The application relates to polymorphisms in the CCR-2 gene and their diagnosis. D7 (see below) discloses the V64I polymorphism of CCR-2 and the effect that this polymorphism has on the delay of the development of AIDS in HIV patients. The requisite unity of invention therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the 13 polymorphisms and the corresponding primers, probes and methods (Guidelines III-7.5; lack of unity "a posteriori").

In conclusion, the present application embraces 14 inventions.

**Section V:**

The following documents are referred to in this communication:

- D1: JP 09 238788 A
- D2: Journal of Biological Chemistry (1997) **272(2)** 1038-1045
- D3: WO 98 06703 (cited in the application)
- D4: Patent Abstracts of Japan JP 09309877 (cited in the application)
- D5: US-A-5707815
- D6: Nucleic Acids Research (1989) **17(7)** 2503-2516
- D7: Science (1997) **277** 959-965

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

**1    Novelty (Art 33(2)PCT):**

- 1.1    Claim 4** is not novel in view of D1 which discloses a human CCR-2 gene sequence comprising a T at position 2385 and an A at position 2649. The same argument applies to **claim 11**.
- 1.2    Claim 9** is not novel, because the use of CCR-2 ligand antagonist drugs and medicaments for treating CCR-2 ligand mediated disease are known from each of D3, D4 (Abstracts) and D5 (col 6 para 2; col 16 para 4-col 17 para 5). The expression "in a human diagnosed as having a single nucleotide polymorphism at one or more positions..." does not specify an allele and does therefore not restrict the treatment to individuals carrying a certain allele of each polymorphism (see also Section VIII below).
- 1.3    Claim 10** is not novel for the following reasons: CCR-2 antagonists and the pharmaceutical application are known (D3/D4: Abstract; D5: col 16 para 4-col 17 para 5). Instructions in a pharmaceutical pack are not considered as being a technical feature.
- 1.4    Claim 1** is novel, because none of the available documents describes a method which comprises the determination of the status of a human by reference to one or more of the CCR-2 polymorphisms. The same argument applies to **claims 2** and **3**.
- 1.5    Claims 5-7** are novel, because none of the available documents discloses allele specific primers/probes for the polymorphisms described in the application.
- 1.6    Claim 8** is novel, because none of the available documents discloses the polymorphic sequences of the present application and CCR-2 antagonists.

**2    Inventive Step (Art 33(3)PCT):**

- 2.1    Claims 1** and **2** do not appear to be inventive for the following reasons:  
Each of D1 and D2 describes the sequencing of the CCR-2 gene (D1: Abstract;

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/02341

D2: p 1039 col 1 para 3) which includes the sequences at positions 2385 and 2649. Since D1 (page 12) discloses the allele containing a T at position 2385 and an A at position 2649 and D2 (GenBank Acc. No U80924) discloses a CCR-2 allele containing a C at position 2385 and a G at position 2649 both allelic forms are already known. Moreover, the diagnosis of the polymorphic alleles does not appear to solve a technical problem because apparently there is no effect linked to the polymorphic alleles.

**Claim 3** does also not appear to be inventive, because ARMS and RFLP are well known methods for the diagnosis of polymorphisms (see documents D6; D7: p 960 col 3; p 964 col 2 note 32).

2.2 **Claim 5:** As the polymorphisms at positions 2385 and 2649 are known from documents D1 and D2 and apparently no effect is linked to either of the different alleles, also claim 5 does not appear to solve a problem. Above all, the detection of polymorphic alleles using allele specific primers appears to be commonplace in the art (e.g. D6). Hence, inventiveness cannot be acknowledged. The same argument applies to **claims 6 and 7**.

2.3 The subject-matter of **claim 8** is distinguished from the closest prior art, D3, in that D3 does not disclose the polymorphisms of the present application. Inventive step cannot be acknowledged for claim 8, because it does not solve a problem. Throughout the application no evidence is found for an effect of the described polymorphisms on the phenotype. There is not indication that the antagonists act differently on the different allelic polypeptides. In addition, the application does not disclose any particular antagonist but refers to published antagonists (application: p 15 l 11-14). It appears therefore that the polymorphic CCR-2 receptors do not show different characteristics compared to the previously studied (D3-D5) allelic receptors. Above all, in step ii) of the claimed method, a CCR-2 ligand antagonist is administered to the "human in need" regardless of the "status of the human by reference to polymorphism".

**Section VII:**

1. The application does not explicitly disclose any CCR-2 ligand antagonist. However, reference is made to a published document (application p 15 l 11-14:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

WO 98/06703 (D3)) which discloses 2-Phenyl benzimidazole derivatives as MCP-1 antagonists. In order for the application to be self-contained at least one CCR-2 ligand antagonist disclosed in D3 should have been incorporated in the description (Guidelines C-II, 4.17).

2. In order for the application to be self-contained (see Guidelines II, 4.17), the reference to non-published patent applications should have been changed to publication numbers throughout the application (e.g. page 5 line 24).
3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.
4. The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 10 line 26) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).

**Section VIII:**

1. **Claims 1, 4-6, 8-10** do not satisfy Art 6 PCT. The reference to sequences in the EMBL database is not sufficient, because entries in databases can be changed after the original submission.
2. **Claims 1, 8 and 9** do not satisfy Art 6 PCT, as the use of the word "polymorphism" is not clear. Claim 1 relates to the diagnosis of a polymorphism in a human. The expression "polymorphism" denotes the phenomenon that more than one allele exist for a gene. In the application 13 polymorphisms of the CCR-2 gene are disclosed each embracing two alleles.  
In a human only the alleles are determined and not a polymorphism. The same argument applies to claims 8 and 9.
3. **Claims 1 and 2** do not meet the requirement of clarity (Art 6 PCT), because they are not consistent. In the first part, claims 1 and 2 refer to a "single nucleotide polymorphism" but in the second part reference is made to an insertion of three nucleotides (ACA at position 41047).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

4. **Claims 8-10** are not supported by the description (Art 6 PCT), because throughout the description no evidence is found for a link between the polymorphisms and CCR-2 ligand mediated disease.



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>PHM 70363/WO</b>		<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/GB99/02341</b>	International filing date (day/month/year) <b>20/07/1999</b>	Priority date (day/month/year) <b>25/07/1998</b>		
International Patent Classification (IPC) or national classification and IPC <b>C12Q1/68</b>				
Applicant <b>ZENECA LIMITED et al.</b>				

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>27/01/2000</b>	Date of completion of this report  <b>07.11.2000</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Tilkorn, A-C</b>  Telephone No. <b>+49 89 2399 8688</b>



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02341

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

**Description, pages:**

1-26 as originally filed

**Claims, No.:**

1-11 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 8 and 11 with respect to industrial application.

because:

- ☒ the said international application, or the said claims Nos. 8 and 11 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02341

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  
- ☐ no international search report has been established for the said claims Nos. .

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02341

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	1-3,5-8
	No:	Claims	4,9-11
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	-

### 2. Citations and explanations

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

**Section I:**

This Preliminary Report also takes into consideration pages 1-4 of the Sequence Listing (i.e information concerning SEQ ID NOs 1-14).

**Section III:**

For the assessment of the present **claim 8** on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Claim 11** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT since it amounts to mere presentation of information (Guidelines IV-2.4(e)).

Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of **claims 8 and 11** (Article 34(4)(a)(i) PCT).

**Section IV:**

"A priori" the application contains two separate inventions:

1. The diagnosis of CCR-2 polymorphic sequences, primers and probes (**claims 1-7, claim 8 (partially) and claim 11**).
2. CCR-2 ligand antagonist drugs and their use (**claim 8 (partially), claims 9 and 10**).

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

The first invention provides a method for the diagnosis of CCR-2 polymorphisms  
The second invention solves the problem of treating a CCR-2 ligand mediated disease.

Throughout the application there is no indication found which would link a certain polymorphic CCR-2 allele to a CCR-2 ligand mediated disease. Hence, the effect of CCR-2 ligand antagonists (invention 2) is not dependent on the polymorphic CCR-2 allele detected in the first invention. Thus, the two inventions do not share a special technical feature.

Furthermore, in view of the prior art, the first invention as defined above (**Claims 1-7, 8 (partially) and 11**) is split up into the 13 polymorphisms and the corresponding primers, probes and methods (lack of unity "a posteriori")(Rule 13.2 PCT):

The application relates to polymorphisms in the CCR-2 gene and their diagnosis. D7 (see below) discloses the V64I polymorphism of CCR-2 and the effect that this polymorphism has on the delay of the development of AIDS in HIV patients. The requisite unity of invention therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the 13 polymorphisms and the corresponding primers, probes and methods (Guidelines III-7.5; lack of unity "a posteriori").

In conclusion, the present application embraces 14 inventions.

**Section V:**

The following documents are referred to in this communication:

- D1: JP 09 238788 A
- D2: Journal of Biological Chemistry (1997) **272(2)** 1038-1045
- D3: WO 98 06703 (cited in the application)
- D4: Patent Abstracts of Japan JP 09309877 (cited in the application)
- D5: US-A-5707815
- D6: Nucleic Acids Research (1989) **17(7)** 2503-2516
- D7: Science (1997) **277** 959-965

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02341

**1    Novelty (Art 33(2)PCT):**

- 1.1 **Claim 4** is not novel in view of D1 which discloses a human CCR-2 gene sequence comprising a T at position 2385 and an A at position 2649. The same argument applies to **claim 11**.
- 1.2 **Claim 9** is not novel, because the use of CCR-2 ligand antagonist drugs and medicaments for treating CCR-2 ligand mediated disease are known from each of D3, D4 (Abstracts) and D5 (col 6 para 2; col 16 para 4-col 17 para 5). The expression "in a human diagnosed as having a single nucleotide polymorphism at one or more positions..." does not specify an allele and does therefore not restrict the treatment to individuals carrying a certain allele of each polymorphism (see also Section VIII below).
- 1.3 **Claim 10** is not novel for the following reasons: CCR-2 antagonists and the pharmaceutical application are known (D3/D4: Abstract; D5: col 16 para 4-col 17 para 5). Instructions in a pharmaceutical pack are not considered as being a technical feature.
- 1.4 **Claim 1** is novel, because none of the available documents describes a method which comprises the determination of the status of a human by reference to one or more of the CCR-2 polymorphisms. The same argument applies to **claims 2** and **3**.
- 1.5 **Claims 5-7** are novel, because none of the available documents discloses allele specific primers/probes for the polymorphisms described in the application.
- 1.6 **Claim 8** is novel, because none of the available documents discloses the polymorphic sequences of the present application and CCR-2 antagonists.

**2    Inventive Step (Art 33(3)PCT):**

- 2.1 **Claims 1** and **2** do not appear to be inventive for the following reasons:  
Each of D1 and D2 describes the sequencing of the CCR-2 gene (D1: Abstract;

D2: p 1039 col 1 para 3) which includes the sequences at positions 2385 and 2649. Since D1 (page 12) discloses the allele containing a T at position 2385 and an A at position 2649 and D2 (GenBank Acc. No U80924) discloses a CCR-2 allele containing a C at position 2385 and a G at position 2649 both allelic forms are already known. Moreover, the diagnosis of the polymorphic alleles does not appear to solve a technical problem because apparently there is no effect linked to the polymorphic alleles.

**Claim 3** does also not appear to be inventive, because ARMS and RFLP are well known methods for the diagnosis of polymorphisms (see documents D6; D7: p 960 col 3; p 964 col 2 note 32).

2.2 **Claim 5:** As the polymorphisms at positions 2385 and 2649 are known from documents D1 and D2 and apparently no effect is linked to either of the different alleles, also claim 5 does not appear to solve a problem. Above all, the detection of polymorphic alleles using allele specific primers appears to be commonplace in the art (e.g. D6). Hence, inventiveness cannot be acknowledged. The same argument applies to **claims 6 and 7**.

2.3 The subject-matter of **claim 8** is distinguished from the closest prior art, D3, in that D3 does not disclose the polymorphisms of the present application. Inventive step cannot be acknowledged for claim 8, because it does not solve a problem. Throughout the application no evidence is found for an effect of the described polymorphisms on the phenotype. There is not indication that the antagonists act differently on the different allelic polypeptides. In addition, the application does not disclose any particular antagonist but refers to published antagonists (application: p 15 I 11-14). It appears therefore that the polymorphic CCR-2 receptors do not show different characteristics compared to the previously studied (D3-D5) allelic receptors. Above all, in step ii) of the claimed method, a CCR-2 ligand antagonist is administered to the "human in need" regardless of the "status of the human by reference to polymorphism".

## **Section VII:**

1. The application does not explicitly disclose any CCR-2 ligand antagonist. However, reference is made to a published document (application p 15 I 11-14:



WO 98/06703 (D3)) which discloses 2-Phenyl benzimidazole derivatives as MCP-1 antagonists. In order for the application to be self-contained at least one CCR-2 ligand antagonist disclosed in D3 should have been incorporated in the description (Guidelines C-II, 4.17).

2. In order for the application to be self-contained (see Guidelines II, 4.17), the reference to non-published patent applications should have been changed to publication numbers throughout the application (e.g. page 5 line 24).
3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.
4. The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 10 line 26) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).

**Section VIII:**

1. **Claims 1, 4-6, 8-10** do not satisfy Art 6 PCT. The reference to sequences in the EMBL database is not sufficient, because entries in databases can be changed after the original submission.
2. **Claims 1, 8 and 9** do not satisfy Art 6 PCT, as the use of the word "polymorphism" is not clear. Claim 1 relates to the diagnosis of a polymorphism in a human. The expression "polymorphism" denotes the phenomenon that more than one allele exist for a gene. In the application 13 polymorphisms of the CCR-2 gene are disclosed each embracing two alleles.  
In a human only the alleles are determined and not a polymorphism. The same argument applies to claims 8 and 9.
3. **Claims 1 and 2** do not meet the requirement of clarity (Art 6 PCT), because they are not consistent. In the first part, claims 1 and 2 refer to a "single nucleotide polymorphism" but in the second part reference is made to an insertion of three nucleotides (ACA at position 41047).

**INTERNATIONAL PRELIMINARY**

International application No. PCT/GB99/02341

**EXAMINATION REPORT - SEPARATE SHEET**

---

4. **Claims 8-10** are not supported by the description (Art 6 PCT), because throughout the description no evidence is found for a link between the polymorphisms and CCR-2 ligand mediated disease.

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year)  
 24 February 2000 (24.02.00)

International application No.  
 PCT/GB99/02341

Applicant's or agent's file reference  
 PHM 70363/WO

International filing date (day/month/year)  
 20 July 1999 (20.07.99)

Priority date (day/month/year)  
 25 July 1998 (25.07.98)

## Applicant

SMITH, John, Craig et al

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

27 January 2000 (27.01.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PHM 70363/WO</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/ 02341</b>	International filing date (day/month/year) <b>20/07/1999</b>	(Earliest) Priority Date (day/month/year) <b>25/07/1998</b>
Applicant <b>ZENECA LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 99/02341

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02341

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 01, 30 January 1998 (1998-01-30) & JP 09 238688 A (TAKEDA CHEM IND LTD), 16 September 1997 (1997-09-16)	4
Y	* see especially nucleotides at polymorphic positions 780 and 1044 * abstract; figure 1 ---	1-3,5,6, 8-11
X	SMITH ET AL: "Contrasting genetic influence of CCR2 and CCR5 variants on HIV -1 infection and disease progression" SCIENCE, vol. 277, 15 August 1997 (1997-08-15), pages 959-965, XP002099015 ISSN: 0036-8075	5,6
Y	* see especially point 31 of the notes * the whole document --- -/--	1,2



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

22 February 2000

Date of mailing of the international search report

07. 03. 2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Knehr, M

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOSTRIKIS ET AL: "A chemokine receptor CCR2 allele delays HIV -1 disease progression is associated with a CCR5 promoter mutation" NATURE MEDICINE, vol. 4, no. 3, March 1998 (1998-03), pages 350-353, XP002099017 ISSN: 1078-8956 cited in the application	5,6
Y	the whole document	1,2
X	--- WONG L-M ET AL.: "Organization and differential expression of the human monocyte chemoattractant protein 1 receptor gene" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 2, 1997, pages 1038-1045, XP002121129 cited in the application the whole document & DATABASE GENBANK 'Online! Accession number (AC): U80923, 1997 WONG L M ET AL.: "Organization and differential expression of the human monocyte chemoattractant protein 1 receptor gene" * see especially nucleotides at polymorphic positions 42673 and 42874 * abstract	4
X	--- DATABASE GENBANK 'Online! Accession number (AC): T40384, 1995 HILLIER L ET AL.: "The WashU-Merck EST project" XP002131229 * see especially nucleotides at polymorphic position 41768 * abstract	4
Y	--- SOZZANI S ET AL: "MCP -1 and CCR2 in HIV infection: regulation of agonist and receptor expression" JOURNAL OF LEUKOCYTE BIOLOGY, vol. 62, July 1997 (1997-07), pages 30-33, XP002099019 ISSN: 0741-5400 the whole document	8-10
Y	--- US 5 707 815 A (CHARO ISRAEL F ET AL) 13 January 1998 (1998-01-13) cited in the application the whole document --- -/--	8-10

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02341

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MUMMIDI S ET AL.: "Genealogy of the CCR5 locus and chemokine system gene variants associated with altered rates of HIV-1 disease progression" NATURE MEDICINE, vol. 4, no. 7, 1998, pages 786-793, XP002121126 abstract page 786, column 1, paragraph 1 -column 2, paragraph 2 page 789, column 2, paragraph 2 -page 792, column 2, paragraph 3; figure 1; tables 1-3 -----	1,5,6
Y	WO 97 40462 A (SPECTRA BIOMEDICAL INC) 30 October 1997 (1997-10-30) cited in the application the whole document ---	11
Y	NEWTON C R ET AL: "ANALYSIS OF ANY POINT MUTATION IN DNA. THE AMPLIFICATION REFRACTORY MUTATION SYSTEM (ARMS)" NUCLEIC ACIDS RESEARCH, vol. 17, no. 7, 11 April 1989 (1989-04-11), pages 2503-2516, XP000141596 ISSN: 0305-1048 the whole document ---	1,3
A	ANZALA A O ET AL.: "CCR2-64I allele and genotype association with delayed AIDS progression in african women" THE LANCET, vol. 351, 1998, pages 1632-1633, XP002121127 the whole document ---	
A	RIZZARDI G P ET AL.: "CCR2 polymorphism and HIV disease" NATURE MEDICINE, vol. 4, no. 3, 1998, pages 252-253, XP002121128 the whole document -----	



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02341

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 09238688 A	16-09-1997	NONE	
US 5707815 A	13-01-1998	AU 1679395 A EP 0740701 A JP 9508264 T WO 9519436 A	01-08-1995 06-11-1996 26-08-1997 20-07-1995
WO 9740462 A	30-10-1997	AU 2734197 A EP 0897567 A	12-11-1997 24-02-1999